TRIP REPORT

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EPIDEMIOLOGY AND FIELDWORK

Visit to Kiev, Ukraine - May 18, 1998 to June 7, 1998

I. STUDY OF LEUKEMIA AND OTHER HEMATOLOGICAL DISEASES AMONG CLEAN-UP WORKERS IN UKRAINE FOLLOWING THE CHERNOBYL ACCIDENT

A. Visit to Dnipropetrovsk Oblast

① Background: Prior to the plenary session and meetings with Drs. Beebe, Howe and other NCI staff and consultants, a group of investigators from Ukraine together with myself and Drs. Finch and Masnyk traveled to the oblast of Dnipropetrovsk in order to familiarize ourselves with study procedures being followed in the field. The Ukrainian investigators traveling with us included Drs. Bebeshko, Dyaghil and Gudzenko.

The oblast of Dnipropetrovsk had been chosen by the Ukrainian investigators to implement and complete Phase 1 of the study in Ukraine The primary objectives of Phase 1 of the leukemia/lymphoma study in clean-up workers is to determine the feasibility of procedures to identify and follow-up the larger cohort and to assess the availability of the appropriate clinical records together with pre-treatment biological material for clean-up workers in order to determine leukemia/lymphoma disease status.

② Hospital Visits: During our two day stay in Dnipropetrovsk oblast the Ukrainian investigators took us to a number of area hospitals in the cities of Dnipropetrovsk and Kryvyi Rig including oblast, city and raion hospitals some of which specialized in treatment of hematological diseases of clean-up workers. At the latter institutions we were introduced to medical staff who were

responsible for the initial diagnoses and treatment of hematological diseases in clean-up workers residing in Dnipropetrovsk oblast at the local area.

At all the institutions visited our questions regarding case identification and possible follow-up procedures of clean-up workers were answered. However often elaborate and confusing explanations were given of the organization of the medical care system in Ukraine at the oblast, city and raion level.

③ Hospital Number 3: We visited a local area hospital (designated hospital number 3) which is a regional raion hospital in the sense that all clean-up workers in the immediate area attend the polyclinic at this hospital for their annual examination as part of the Ukrainian health care system's follow-up of clean-up workers. We were told that in this raion, for example, there were approximately 600 clean-up workers in total registered in the Chernobyl State Registry who attended the polyclinic for examination and that such attendance was 100 percent owing to the fact that most of the staff in this polyclinic had worked in the clinic for a number of years and personally knew the clean-up workers.

④ Oblast Hospital: At the major oblast hospital in the city of Dnipropetrovsk we again were introduced to medical staff from the highest administrative levels to the staff responsible for the diagnoses and treatment of clean-up workers attending the hospital. It was at this hospital that we were introduced to Dr. Tatiana Chekmareva who is responsible for the management of case identification and follow -up at the Dnipropetrovsk oblast level.

⑤ Present Status of Clean-Up Workers in Dnipropetrovsk Oblast: In discussions with Dr. Natalia Gudzenko and Dr. Tatiana Chekmareva it was determined that approximately 18,000 of the clean-up workers registered in the Chernobyl State Registry who first worked at Chernobyl between 1986 and 1990 are currently resident in Dnipropetrovsk oblast.

⑥ Follow-up of the 18,000 Clean-up Workers: During the past year approximately 14,000 clean-up workers attended their local polyclinics in Dnipropetrovsk oblast for their annual examination. For the remaining 4000 clean-up workers, approximately half of them had been examined during the past two years while 600 had not come for their annual examination for the last three years, 300 for the last four years, and another 600 for five years or more. Drs. Gudzenko and Chekmareva anticipated that the majority of the 2000 who had not been examined during the past two years will re-appear for their annual examination. On this basis, the medical examination system of clean-up workers in Dnipropetrovsk oblast has current medical and personal identifying information on approximately 85% of the cohort.

⑦ Pilot Project to Trace and Examine Clean-up Workers Lost to Follow-up: During our visit to the Dnipropetrovsk oblast registry the pilot project to trace and examine clean-up workers identified as lost to follow-up in Dnipropetrovsk oblast was discussed. Professor Burch and Drs. Beebe, Howe, Gudzenko and Chekmareva met subsequently in Kiev regarding the pilot study, the details of which are discussed in Section D1.

⑧ Present Status of Clean-up Workers in Other Oblasts and City of Kiev: At the meeting at the Dnipropetrovsk oblast registry the possible ascertainment of the other members of the entire cohort of clean-up workers from the remaining oblasts and Kiev city was discussed. The general agreement among the Ukrainian investigators was that the follow-up of clean-up workers resident in the oblasts of Donetsk, Kharkiv and Sumskaya would probably be similar to that in Dnipropetrovsk. It was suggested however that this will not be the case for Kiev oblast and Kiev City. It was suggested that the successful maintenance of continued follow-up of clean-up workers by regular attendance at annual examinations in Donetsk, Dnipropetrovsk, Kharkiv, and Sumskaya oblasts may be partially due both to the stable nature of the populations in these oblasts and the stability of medical staff in these oblasts where there is a minimum of job turnover allowing the medical staff to become acquainted on a personal level with the clean-up workers. Furthermore, it was learned that for Kiev

oblast identical data was sent to the Chernobyl State Registry for two years but this has since been rectified.

SUGGESTION: It was suggested that the appropriate personnel in the other oblasts and Kiev City be contacted at an official level so that tabulations can be run in each oblast for clean-up workers not re-attending polyclinics for their re-examinations.

⑨ Overall Impressions of Trip to Dnipropetrovsk Oblast: I was very impressed with the enthusiasm and cooperation of the medical staff at oblast and raion hospitals and at area polyclinics. However, despite meeting a wide variety of medical personnel at various levels of case management at these facilities and familiarizing myself with regard to how clean-up workers are entered into the medical system I was disappointed that I did not see any real field work procedures taking place.

B. Plenary Session. May 20, 1998
Research Center for Radiation Medicine, Academy of Medical Sciences of Ukraine, Kiev

The plenary session was chaired by Dr. A. Romanyenko, Project Director. Heads of each sub-division in the project commented on their division's progress to date. Details of this progress are included in the progress report which was supplied at the session.

C. Meeting with Drs. Dyaghil, Gudzenko, Finch and Klimenko, May 21, 1998

① Diagnostic Review: I met with Drs. Dyaghil, Gudzenko, Finch and Klimenko to discuss the need to ascertain as soon as possible the extent to which biological material will be available for diagnostic assessment for cases with leukemias/lymphomas in Phase II of the study and to organize the procedures to be followed by a yet to be appointed panel of hematologists/pathologists to review retrospective diagnoses of such cases in the Ukraine. It is my understanding that once this panel has been appointed it is essential that they gain some experience working together as a cohesive group so that, if Phase II of the study is implemented, they can continue to review the diagnoses of cases with leukemias, lymphomas and related disorders as they emerge in the ongoing cohort study.

A direct result of the meeting was that Professor Burch and Dr. Gudzenko subsequently are preparing a draft protocol to be followed in initiating the pathological review process which includes suggestions from Drs. Beebe, Finch and Howe. A copy of this draft protocol will be included in the Columbia sub-contract third quarterly report.

② Brief Description of Draft Protocol for Pathological Review of Retrospective Diagnoses of Leukemias/Lymphomas in the General Ukrainian Population:

- A diagnostic review is planned by a panel of expert hematologists/pathologists of both deceased and alive patients with diagnoses of leukemias, lymphomas and/or related diseases chosen from the general population of the Ukraine;

- The general Ukrainian population has been chosen for the basis of this review on the assumption (confirmed by Drs. Dyaghil and Klimenko) that the general population diagnosed with these diseases is not treated any differently than clean-up workers diagnosed with the same diseases in terms of diagnostic procedures and medical treatment;

- A random sample of cases with diagnoses of leukemias/lymphomas and related diseases will be chosen from oblast and hematological clinics of the same oblasts and other areas to be included in Phase II of the study. The sample will be based on different diagnostic categories among male cases in the defined age group of 20 to 40 years of age between 1986 and 1990 so that age at diagnosis should be comparable to that for the cleanup workers. The number of required cases in each sub-classification was determined by Drs Dyaghil and Finch;

- Approximately 20 cases diagnosed with leukemia/lymphoma and related diseases for the period 1987 to 1997 will be chosen from each of the following oblasts and study areas:

Dnipropetrovsk, Donetsk, Kharkiv, Kiev, Sumskaya and Kiev city giving a total of 60 cases for review;

- All clinical records, laboratory reports, pre-treatment blood, bone marrow/tissue samples, stains etc. will be requested from the medical facility at which each case was diagnosed and will be sent to Kiev for review;

- As far as possible, all clinical and biological material for each case will be "blinded" in order to reduce any bias on the part of the diagnostic reviewer;

- The purpose of the review essentially is to determine the availability of clinical and biological material for cases diagnosed with leukemias/lymphomas and related diseases together with giving the review team some experience working together. The review will not be able to identify false negative cases but will be able to identify false positives;

- Once the review has been completed all clinical and biological material will be sent back to the originating medical facility;

- Professor Burch and Dr. Gudzenko will take responsibility for the further development of the review protocol in collaboration with the hematologists involved and will organize and manage the review process itself which is tentatively planned for no later than January 1999;

- Membership of the review panel should be determined no later than the end of August, 1998 and it is anticipated that at the very least the panel will consist of one hematologist expert in leukemia morphology from both the USA and Ukraine, one hematopathologist expert in leukemia/lymphoma from both the USA and Ukraine, and one hematologist and/or hematopathologist from France.

Further development of the review protocol and organization of the review process itself will be the responsibility of Professor Burch together with Dr. Gudzenko.

D. Further Meetings with Dr. Gudzenko (and Later with Drs. Beebe and Howe) May 22 - June 6, 1998

① Pilot Project in Dnipropetrovsk Oblast to Trace and Bleed Sub-Sample of Clean-Up Workers: At our earlier meeting in Dnipropetrovsk oblast it was determined that 40 clean-up workers had been identified randomly from the Chernobyl State Registry as both resident in Dnipropetrovsk oblast and having up to date identifying information (i.e. they have been in attendance for their annual medical examination). It was originally planned to pre-test the pilot phase 1 study procedures by inviting this group of individuals to the oblast polyclinic for dosimetry questionnaire administration with a subset of these individuals then being asked to have their blood drawn.

However, it is essential in the pilot phase 1 study to not only assess the viability of study procedures in cohort members who are compliant with the ongoing annual medical examinations system but also to assess these same procedures amongst clean-up workers who have not been examined and therefore may be considered as lost to follow-up.

SUGGESTION: It was suggested that in addition to the original group of clean-up workers identified as living in Dnipropetrovsk oblast and having up to date identifying information that another random sample of clean-up workers (approximately 50) be chosen amongst those clean-up workers who have not been in attendance for their annual examination for one or more years and that this sample should be stratified by years of not being in attendance at the annual medical examination (ie. years of lost to follow-up) so that the number in each of those years is proportional to the total numbers in those years.

② Tracing, Questionnaire Administration and Collection of Blood Samples in Pilot Project: Attempts should be made to trace as many as possible of those clean-up workers who have been identified as being lost to follow. Of those who are subsequently traced a random sample of ten should be invited to come to the oblast polyclinic for questionnaire administration and blood collection. If some of these individuals do not show up for examination after the invitation, the invitation could be sent to another group of traced individuals until a total of ten clean-up workers from the the lost to follow-up group have participated in the questionnaire administration and blood collection. All members of the randomly selected group of clean-up workers previously identified as being under current observation should be invited to attend the oblast polyclinic for questionnaire administration and blood collection with the target being having questionnaire and blood specimens for 30 of this group so that the total number of clean-up workers with questionnaire information and blood collection will number 40. However, since the taking of blood samples from individuals and subsequently only processing 10 of them may be regarded as unethical a random sample of blood collection could be taken from the 40 individuals who have supplied questionnaire administration.

It was agreed that Dr. Tatiana Chekmareva, who is managing the Dnipropetrovsk Oblast Registry, be responsible for the initiation of the pilot project in Dnipropetrovsk. It is essential that all procedures used for tracing the lost to follow group and invitations etc. to questionnaire administration and blood collection for both the subsequently traced lost to follow-up group and those currently under observation be clearly documented. The results of all follow-up procedures should be recorded as successful or failures and by year of loss to follow-up. Despite the fact that many of the denominators in the different categories of study procedures may be small, it will be possible to determine response rates for various procedures and therefore assess the extent to which work in the pilot phase I study can assess the possible success of the larger cohort study.

Examples of the kinds of letters that could be sent to clean-up workers to invite them to participate in the study, respond to the dosimetry questionnaire and give permission for blood collection were discussed with both Drs. Gudzenko and Chekmreva together with suggestions for alternate

procedures in order to attain as high a response rate as possible among both the lost to follow up group of clean-up workers and those clean-up workers presently attending medical examination.

SUGGESTION: It was suggested that Professor Burch and/or Dr. Howe travel to Dnipropetrovsk oblast in the fall of 1998 to assess the quality and extent of the work done in this vital phase of the study. Such a trip on Dr. Howe's part may in fact coincide with his tentatively planned trip to Kiev, Ukraine to give a one week practical seminar on probabilistic record linkage (see Section II.C.5. of Dr. Howe's trip report). Additionally, Professor Burch would be able to work at this time with Dr. Gudzenko on the acquisition and organization of the required clinical and biological material for the anticipated diagnostic review of retrospective cases diagnosed with leukemias, lymphomas and related disorders. (A detailed description of this aspect of the study is given in Section C.1. of this trip report.)

E. Active Follow-Up of the Cohort:

Fieldwork Procedures: As per my suggestions for improving fieldwork detailed in my trip report of February 10-12, 1998, the introductory letter to possible cohort members has been simplified, contains a statement to the effect that without the participation of the clean-up worker the study cannot be successful, asks the clean-up worker to inform project staff about any plans he has for moving etc. The fieldwork for the pilot study in Dnipropetrovsk will include my earlier suggestions of involving local health nurses to trace and ask for the participation of clean-up workers, the sending of thank you letters to individuals who choose to participate in the study, etc. I discussed some potential problems with the current version of the dosimetric questionnaire with Dr. Gudzenko and she promised that the epidemiology group will take these into consideration together with any changes that are deemed necessary after the pilot work is completed in Dnipropetrovsk oblast. I was informed that any possibility of administering the dosimetric questionniare at the clean-up worker's home is not acceptable practice in the Ukraine. However, I was reminded that the interviewer in the pilot phase of the study in Dnipropetrovsk oblast, Dr. Chekmareva was one of those interviewers initially trained at a workshop held in Kiev in 1997 where the then current questionnaire was pre-

tested on 15 clean-up workers attending polyclinics in Kiev. I reiterated to Dr. Chekmareva during my present trip of how important it is to ask all questions in the questionnaire as similarly as possible to all respondents.

F. Passive Follow-Up of the Cohort:

① Other Data Sources: My earlier suggestions of tracing lost to follow up clean-up workers through other data bases were reiterated in meetings with Drs. Beebe, Gudzenko and myself. In addition to the possibility of using death records amongst clean-up workers identified by local physicians at the oblast polyclinic level through manually searching such records the need to approach other sources of information was stressed. These include the Ministry of Internal Affairs (i.e. the passport office), the "benefits file" from the Ministry of Chernobyl Affairs, and an as yet unidentified source which presumably maintains a file of "lifetime events". Despite the fact that these possible sources of information cannot be tested during the pilot phase it is imperative that they be officially approached during the pilot phase at a senior level, i.e. through Dr. Romanyenko's office, to determine what information is available, the extent to which the information is computerized and if it is possible for our study to access this information.

② Record Linkage: Details of the implementation of record linkage between the existing files with information on the clean-up workers is detailed by Dr. Howe in his trip report (See Section II,C. Points 1 to 5).

G. Overall Summary:

The three most essential requirements for the study investigators to concentrate on at this time are the determination of the feasibility of establishing and tracing the cohorts, the ability to establish reasonably accurate dose estimates for members of the cohorts and the determination of the existence of, and practical review of, essential clinical and biological material on clean-up workers diagnosed with leukemias, lymphomas and related disorders. With regard to the first requirement which is more particularly in my field of expertise I was somewhat disappointed in the seeming lack of any

practical fieldwork procedures having been initiated in the pilot phase I study in Dnipropetrovsk oblast. Therefore, one of the top priorities from my perspective is the immediate initiation and careful documentation of follow-up and pilot testing of study procedures in this oblast. In this respect I was impressed with the capabilities and demeanor of Dr. Chekmareva, who is responsible for this task in Dnipropetrovsk oblast over the next couple of months. Finally, with regard to the third requirement to establish the existence of appropriate clinical and biological material for successful diagnostic review in Ukraine I have established an excellent working and personal relationship with Dr. Gudzenko and am confident that she and I will be able to work towards confirming the availability of the relevant material for diagnostic review together with organizing and directing the work of a diagnostic review panel.

May 25, 1998 to June 6, 1998

II. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN UKRAINE FOLLOWING THE CHERNOBYL ACCIDENT

A. May 25, 1998 Meeting with Dr. A. Derevyanko, Head of Epidemiology Group and Dr. V. Tereschenko, Vice-Director of Institute of Endocrinology and Metabolism, Deputy Director of Project.

① Prior to the plenary session of the study which met on June 3, 1998 I met with Drs. Derevyanko and Tereschenko and reviewed progress to date particularly with respect to fieldwork accomplished in the pilot raion of Ivankiv.

② Background: A 20,000 member cohort of children who were between the ages of zero and eighteen years in 1986 has been established chosen by dose category with approximately 10,000 in the high dose range, and 5000 each in the two lower ranges. (This list of children is referred to as the Likhtarev list). This cohort of children were resident in raions of the oblasts of Chernihiv, Kiev and Zhytomyr at the time of the accident.

③ Two mechanisms to date have been utilized to locate the current addresses of this cohort: manual searching of records at local medical institutions and linkage of the dose file (Likhtarev list) with the Ukrainian State Chernobyl Registry (Dr. Cortushin, Director, Ukrainian Center of Information Technology and Chernobyl State Registry). It is my understanding that these two methods have been done for a number of raions with varying success rates (some as low as 5 percent, others as high as almost 90 percent). Dr. Derevyanko has informed me however that for the raions other than Ivankiv the numbers for the manual searches have not as yet been entered into the computer and therefore it is not possible at the present time to determine which of the two mechanisms for updating current information on the cohort is the best.

④ Ivankiv Raion: For Ivankiv raion, which has been chosen by the investigators as a "pilot" raion, linkage between the Chernobyl State Registry and the Likhtarev List has found approximately 50 percent of the cohort members while manual searching of medical records in local institutions has found 40 percent. However, it is important to remember that these two categories do in fact overlap and are not mutually exclusive.

The progress to date in determining current addresses for children living in Ivankiv raion has not in fact changed since my first trip in February, 1998. There are current addresses (as far as it can be known) available for 494 (70 percent) of the total 737 potential cohort members who were between zero and eighteen years old at the time of the Chernobyl accident who are still resident in Ivankiv raoin). Therefore, current addresses are still unaccounted for 243 of the cohort (30 percent) in Ivankiv raion.

Results of Interviewing/Examination Fieldwork to Date - May 25, 1998:

Letters of invitation to potential participants in the study were sent in January of this year to the 494 individuals with known current addresses. In point of fact, these invitation letters were not sent by mail to these individuals but rather they were personnally delivered to them by local area medical staff. The letters explained the nature of the study to the potential cohort members and requested them to send back to study headquarters a postcard which had been attached to the letter indicating their response to the invitation.

As of May 25, 1998, 146 agreed to participate in the study, 4 absolutely refused and there was no response from 344.. Subsequently, the local medical staff re-approached the non-responders and asked them in person to participate in the study. Evidently, of these, approximately 80 percent indicated that they would participate in the study.

Mobile Team: Since my first visit to Kiev in February of 1998 one mobile team has been established and this team has travelled to Ivankiv raion in April and May to recruit and therefore interview and examine cohort members with the final result that 160 cohort members in Ivankiv raion have been recruited, interiewed and examined. It is my understanding that the mobile team is continuing its work in Ivankiv raion so these numbers should improve.

SUGGESTION: As per my concern expressed in my first trip report, that too much leeway has been given to the Ivankiv local area medical staff in implementing the study in this raion it is apparent that there is little or no documentation to date of the on-going study procedures. Without such documentation it is impossible, for example, to determine which recruitment procedures work best and which methods should be dropped owing to poor response etc. It is absolutely essential that all study procedures used and success rates of the various approaches used by project staff to trace and recruit cohort members is carefully documented. It has been suggested by Dr. Derevyanko that obtaining accurate counts of various procedures used in Ivankiv raion to date may possibly never be available from medical staff.

⑤ Recruitment of Evacuees From Prypiat Living in Kiev: Drs. Derevyanko and Tereschenko explained that when the Likhtarev File was linked to the Chernobyl Registry a number of children who were evacuated from the Prypiat area were found to have current addresses in Kiev. A list of these children, numbering 542, was subsequently sent to the Computer Center of the Kiev City Department of Public Health and current addresses in Kiev were found for 413 potential cohort members.

As of the first week in May, 1998 the epidemiology group has been approaching these individuals by telephone, inviting them to be examined and interviewed at the Institute of Endocrinology and Metabolism. To date (May 25, 1998), 74 individuals have been recruited into the study and given the interview and examined. As this aspect of the study has just begun there has not as yet been any

tabulations of response rates. In this regard however I did stress to Drs. Derevyanko and Tereschenko the importance of documenting all procedures being used for tracing and recruiting cohort members by telephone in this group of individuals.

⑥ Related Activities Since February 1998 Trip:

a. Updating of Identifying Information on Cohort Members Lost to Follow-Up: As mentioned above, in Ivankiv raion there is no current address information available for 243 of 737 potential cohort members ie. 30 percent of the cohort. In this regard, the Ukrainian Ministry of Health has requested government officials in the Ministry of Internal Affairs (passport office) for all known current addresses known in their files of children who are listed on the Institute of Radiation file (the Likhtarev file) in Ivankiv and all other raions in the study. This request was in fact made quite some time ago and I suggested that the request be followed up immediately.

b. I was encouraged to learn that attempts have been made by the Epidemiology Group to publicize the study. Dr. Tereschenko wrote a description of the Thyroid Study which was published on April 1, 1998 in a medical newspaper that most medical workers have available to them. In addition a somewhat briefer description of the study appeared in the April 10, 1998 edition of a local newspaper in Ivankiv raion.

B. Further Meetings With Drs. Beebe, Derevyanko, Mitchell and Howe, June 3 to June 6, 1998

As a result of our meetings I will comment and make suggestions on the following areas in the implementation of the study in Ukraine:

- the establishment and ascertainment of the cohort including follow-up;
- the in utero study;
- the general area of fieldwork including letters of invitation to potential cohort members, questionnaires, interviewer training, interview monitoring;
- the documentation of study procedures;
- coding and data entry;

① Establishment and Ascertainment of the Cohort Including Follow-Up: The Data Control Center indicated in the plenary session of June 3, 1998 that after linking the dose file (i.e. the Likhtarev file) with the Chernobyl State Registry that approximately 4800 of the 20,000 cohort was found ie. only 25 percent of the cohort. Additionally, as noted above specifically for the Ivankiv "pilot" raion, after utilizing both this mechanism and manual searches of local medical records, 30% of potential cohort members in this raion were unaccounted for.

In this regard Dr. Howe has suggested that it would be possible to introduce a probabilistic record linkage system into the Chernobyl State Registry that might reduce any problems arising from the previously conducted matching between the Likhtarev file and the Chernobyl State Registry file. He would conduct a training workshop in Kiev at the registry utilizing practical ready made software to conduct linkages and he hopes that this mechanism might determine whether there is any data missing in the Chernobyl Registry for individuals from the Likhtarev file.

SUGGESTION: I would suggest that in addition to the initiation of new improved linkages between the Likhtarev file and the Chernoyl State Registry file that as soon as possible linkages be made to other existing database files in Ukraine. In this regard the Ministry of Health's request to the Ministry of Internal Affairs (passport offices) to help in determining current addresses the passport, offices may have for individuals on the dose file should be followed-up immediately.

SUGGESTION: With regard to follow-up of cohort members who attend screening and are administered the dosimetry and medical history questionnaires it is essential that at the time of screening and questionnaire administration cohort members be asked to give identifying information such as addresses and telephone numbers for their parents, other relatives or potential contact persons such as older friends as well as some kind of indication of any plans they may have for re-locating. The initiation of these procedures immediately is necessary if future contact with the cohort members is to be successful.

SUGGESTION: In order to facilitate continued follow-up of cohort members who are currently being entered into the study it is essential (as I mentioned in my first trip report) that thank you letters be sent to individuals following their attendance at screening and interviewing. It is my understanding that, owing to lack of computer facilities at the present time, this has in fact not been done for those recruited to date.

② In utero study: The planned in utero study was discussed briefly. To date, evidently little has been undertaken in this study except for linking a list kept by the Institute of Pediatrics with the dose measurement file. The "matching" rate was reported to be only 16%.

SUGGESTION: As suggested in both the study of leukemia amongst cleanup workers in Ukraine and thyroid cancer in children in Belarus, Dr. Howe would conduct a training workshop in Kiev on probabilistic record linkage. The use of this system may well improve linkage between the pediatric and dose measurement files.

③ Fieldwork:

Invitation Letter: I was encouraged to learn that as a consequence of my first trip to Kiev in February of this year that the letter of invitation to potential cohort members was to some extent modified to make it more "user friendly" by simplifying medical terminology, inviting the potential respondents to telephone the study center with any questions they may have etc.

SUGGESTION: However, as a consequence of familiarizing myself with the work of the mobile team and other on-going fieldwork procedures since that first trip, other changes to the invitation letter are necessary as well as determing when it should be sent to potential respondents:

- In order to facilitate the collection of fasting blood samples the invitation letter should be sent out to potential cohort members further in advance and should include a statement that a fasting type of blood collection will be requested;

- The mobile team indicated that for children who were less than 10 years of age at the time of the Chernobyl accident questionnaire information on a number of factors such as history of illnesses in relatives and dose information around the time of the accident was inadequate. I would suggest therefore that the invitation letter to potential cohort members include a statement to the effect that the parents of the child come to the examination with the child if possible, that if this can be done that the parent (or other relative, guardian etc) be that person who knows the most about the child at the time of the accident, and most importantly, that the subject areas covered by the questionnaire be indicated in the invitation letter so that the child and his/her parents can be better prepared to answer questions.

Questionnaire and Interview:

SUGGESTION: After familiarizing myself with the experience to date of the mobile team and the team at the Institute of Endocrinology and Metabolism it is necessary to change the questionnaire in the following ways. First of all, since different questions may be answered by different people depending upon the information sought by the questions it is essential that the questionnaire indicate who or what combination of people answered the questions. It may be too cumbersome to do this on a question by question basis but it could be done by having the interviewer indicate at the end of the questionnaire who gave all the information, who gave the most, whether it was equally answered by, for example, the child and his/her parents etc. Such a description of the interview process could be further specified by indicating who gave most of the anwers etc. to which kinds of questions ie. history of residence, questions on milk consumption etc.

Additionally, it would be a good idea to include at the end of the questionnaire a semi-quantitative assessment of the " reliability" of the information given by the respondent(s). The interviewer could, for example, estimate this "reliability" by indicating on a five point

scale (ranging from very reliable to very unreliable) where the respondent(s)'s answers fit. This estimation could also be done (as above) by types of questions asked. Although this kind of estimation by interviewers is quite subjective it nevertheless can be useful in identifying and therefore eliminating from analysis those questionnaires which appear to be unsatisfactory.

SUGGESTION: The mobile team indicated that cohort members who were over the age of 10 -12 years at the time of the Chernobyl accident responded fairly well to the questionnaire. Therefore, it is essential that a cut-off age below which only questionnaires completed by the knowledgeable parent or other person at the time of the Chernobyl accident be included in the study.

SUGGESTION: It is essential in the interview situation where the cohort member attends but is unable to answer the questions that the procedures followed in having that individual have his/her parents or other knowledgeable person fill out the answers subsequent to attendance at screening be clearly documented and described. Such monitoring of questionniare completion will of course be aided by the inclusion of questions determining who answered what questions as detailed above.

SUGGESTION: Possible procedures that could be initiated to train the interviewers and monitor the interviewing of cohort members were discussed with Dr. Derevyanko including the use of videos (which I am currently assessing at Columbia University), the attendance at interviews by investigators to ensure that compliance with standard interviewing techniques are being followed by all interviewers, re-interviewing of a sub-sample of previously interviewed cohort members , and regular meetings of all interviewers to discuss any problems.

④ Documentation of All Study Procedures:

SUGGESTION: At the moment, especially with respect to the fieldwork being done by the local medical staff in Ivankiv raion, there is little or no documentation of the procedures being used to trace and recruit potential cohort members and success rates for these various procedures. In meetings with Drs. Beebe, Derevyanko and Howe it was suggested that for each potential cohort member a "case location" form be generated by the computer which would enable the investigators to track the progress (or lack of) of each individual in the study (ie. giving details of how the potential cohort member was located, the number and kind of appproaches used to recruit the cohort member, the responses to these different approaches, and the success of these procedures to locate and recruit these individuals).

⑤ Coding and Data Entry: It appears that at the present, none of the information entered on the forms for those recruited and examined to date has been entered into the computer.

SUGGESTION: It is absolutely necessary that coding and data entry be initiated as soon as possible. The reasons for this are twofold. First, if this component of the study is not begun soon, in my experience, studies have a way of "running away from you" and the investigators are swamped with unintelligible data. Second, and more importantly, it is difficult to assess quality control of the data. With respect to coding, it is imperative that a coding manual be compiled and that coding staff be assigned and trained utilizing this manual.

The process of coding forms for data entry can be further facilitated by having as many as possible forms pre-coded. For example, where forms ask for a simple dichotomized answer, e.g., gender, predetermined numerical codes can be assigned on the forms themselves; example: male = 1, female = 2.

SUGGESTION: I have asked Dr. Buglova, Head of the Epidemiology Group in Belarus, to send to Dr. Derevyanko, copies of all the forms used in the Belarussian study, as examples, since many of the BelAm forms have, in fact, been pre-coded.

C. Overall Summary:

I have established an excellent rapport with Dr. Derevyanko and because of this, I am optimistic about our future work together. One of the most essential areas for the study investigators to concentrate on at this time, amongst others, is the documentation of all study procedures (both in the past, if possible, and the future) together with coding and data entry.

Visit to Minsk, Belarus - June 8, 1998 to June 10, 1998

III. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN BELARUS FOLLOWING THE CHERNOBYL ACCIDENT

Dr. V. Stezhko, Director of the Project and Head of the Department of Ministry of Public Health chaired three plenary sessions involving all senior staff of the BelAm project, NCI staff, NCI consultants and the Columbia University contract personnel. My comments and suggestions detailed below are primarily limited to the meetings I had with Dr. Elena Buglova, Head of the Epidemiology Group and her two colleagues Dr. Ludmila Kul'kova and Dr. Alexander Skalizhenko, Mr. Artur Kuvshinnikov, Head of the Data Coordinating Center and Drs. Gil Beebe and Herman Mitchell.

A. Background:

A cohort of approximately 15,000 children (18 years of age or younger at the time of the Chernobyl accident) who had dose measurements taken in 1986 has been identified in eight oblasts of Belarus, including the city of Minsk. This file, which is often referred to as the Moscow file is made up of 8500 children with high doses, and 7500 with medium or low doses. At the time of my first trip to Minsk, Belarus in February of this year, current addresses of approximately 8500 (60 percent) of the cohort had been determined through a combination of two methods i.e. linking the dose measurement list (the Moscow list) with the Chernobyl Registry and through the Chiefs of Medical Structure at the raion level (manual searches of local medical record departments of dispensaries and outpatient clinics).

Letters introducing the study to potential cohort members had been sent to those with known current addresses resulting in 2200 who provisionally agreed to participate with another 6200 unknown status or refused. The great majority of the 6200 with unknown status were potential cohort members who did not respond in any way to the invitation letter or who responded indicating that they could not participate for a number of reasons. A high proportion of this group of cohort

members could include persons with incorrect addresses, but this cannot be confirmed. The absolute refusal rate was approximately 10 percent.

In addition, approximately 3500 of the original 15,000 cohort members had been set aside for consideration later due to the fact that the identifying information on the measurement file (the Moscow file) was considered inadequate for matching to the Chernobyl Registry.

B. June 8, 1998 to June 10, 1998 Meetings with Drs. Beebe, Buglova, Kul'kova, Mitchell, Skalizhenko and Mr. Kuvshinnikov

① Establishment and Ascertainment of the Cohort Including Follow-up: Dr. Buglova indicated that only 29 percent of potential cohort members to date have been found by linking the dose measurement file with the Chernobyl Registry and that the linking with other files, e.g the Bureau of Addresses/Ministry of Internal Affairs, the Office of Technology and the Ministry of Emergency has been problematic.

SUGGESTION: It was suggested that Dr. Howe's probabilitistic record linkage system would be invaluable in improving the linking of the above noted files. The possibility that computer matching may be improved by this superior linkage software was discussed and in this context Dr. Howe has offered to conduct a training workshop in Kiev at the Chernobyl State Registry utilizing practical ready made software to conduct linkages. Since linkage between data sources is somewhat questionable in all three studies (i.e., leukemia/lymphoma cohort of clean-up workers, thyroid in children studies in both Ukraine and Belarus), I would suggest that the personnel who would actually carry out the day to day linking of these files in all three studies attend this workshop in Kiev. Improved record linkage would also undoubtedly improve the linking of the 3500 member cohort (set aside because of inadequate identifying information) with the Chernobyl Registry

Since my first trip to Minsk in February of 1998 the BelAm project has evidently "confirmed" the addresses of approximately 42 percent of the original 15000 cohort by expanding the sources used to identify up to date address information from the manual searching of medical records at the local area and linking the dose measurement file to the Chernobyl Registry to other sources such as the Ministry of Internal Affairs (Bureau of Addresses) among others.

At the time of our meetings, however, Dr. Buglova was unable to tell us the exact numbers in various sub-categories of search mechanisms. The best estimate that I could come up with is that, of the total number of potential cohort members found with up to date address information, 25 percent were found by the searching of local medical records, 29 percent were found via linkage with the Chernobyl Registry, 33 percent were found through the Ministry of Internal Affairs (actually through the Bureau of Addresses which evidently receives information from the passport offices at the oblast level), and 10 percent from other sources.

Additional sources which have been approached include the school system, the Office of Technology at the national level and the Ministry of Emergency. The school system was found to be of little use since there are no centralized records. The Office of Technology evidently identified only 50 possible cohort members out of a list of 900 children who were found to be in the correct age range, and the results from the Ministry of Emergency to date suggest that this source is only available for children who were evacuated or re-located to Modilov oblast.

SUGGESTION: I have been quite impressed with the tenacity with which the epidemiology group in the BelAm project has approached other data sources as alternative means of identifying potential cohort members and would suggest that this is continued especially in regard to the Bureau of Addresses/Ministry of Internal Affairs.

SUGGESTION: In order to facilitate continued follow-up of cohort members who are currently being entered into the study it is essential (as I mentioned in my first trip report)

that thank you letters be sent to individuals following their attendance at screening and interviewing. It is my understanding that, owing to some friction between the epidemiology group and the DCC, this has, in fact, not been done for those recruited to date.

② In utero study: Dr. Buglova briefly described the work to date in the in utero study. A list of all births in Belarus from April 26, 1986 to January 31, 1987 has been obtained and, on an on-going basis, is being entered into a file which ultimately will be linked to the dose measurement file (the Moscow file). This list includes identifying information about the natural mother, information on the birth, e.g., date, gender of child, outcome (i.e., live birth or stillborn), and address of hospital. Evidently, approximately 100,000 are on this list of which 11,000 (all in the city of Minsk) have been data entered.

SUGGESTION: At the completion of this data entry of the birth list, the linkage between this file and the dose measurement file would be facilitated by the utilization of probabilistic record linkage and by the attendance of those to be involved in this linkage at the suggested record linkage workshop to be held in Kiev.

③ Fieldwork: A total of 4,770 potential cohort members were sent a letter inviting them to participate in the study with the result that 3,576 agreed to participate (by sending in postcards saying they would participate, telephoning in their responses, relaying their intent to participate at the local level through medical personnel). Of those that agreed to participate following this initial letter, 2,692 have been recruited, interviewed and examined. Evidently, the number of recruited and examined cohort members includes 1,820 who are resident in Gomel, of which only a fraction were recruited and examined by the mobile team. The number of refusals is evidently quite small in all study areas.

SUGGESTION: At the present there is in fact little or no documentation of the procedures being used to trace and recruit potential cohort members and success rates for these various

procedures. Furthermore, at the time of our meetings there appeared to be a major problem (depending on who you listen to) with the Data Control Center in terms of entering forms which do have some documentation and then retrieving information back from the DCC. Together with Drs. Beebe and Mitchell a suggestion was made that an administrative file be created for tracking the progress of the cohort from selection through to the various steps in the screening process. At the time of our meetings, Mr. Kuvshinnikov provided us with a copy of the current database that could be modified for this purpose. Dr. Mitchell sketched out a flow chart that represents the kind of information that would be needed and it is my understanding that once this has been refined it will be sent to the BelAm group.

At the time of the meetings in Belarus we had hoped to meet with the mobile team and learn of their experiences in the field as we had been given the opportunity to do so in Ukraine but this did not happen. However, in discussions with Dr. Buglova, several points were raised regarding on-going fieldwork, including the work of the mobile team.

SUGGESTION: First of all I was encouraged to learn that subsequent to my first trip to Belarus in February of this year that the invitation letter to potential cohort members was changed to become more "user friendly. However, letters of invitation should be more specific in terms of what they require of the respondent, e.g., a fasting blood is one example. The invitation letters should indicate that the parents of the child (or some other person) who knows the most about the child at the time of the accident) be responsible for filling out the questionnaire. Additionally, it is absolutely essential that the BelAm forms be changed to indicate who answered which questions or alternatively who answered most of the questions. Also, in order to eliminate questionable data from analysis it would be a good idea to have the interviewers at the time of screening evaluate the reliability of the respondents' answers.

④ Development of Coding Manuals: Evidently, despite the fact that examples of how to fill in forms and appropriate codes are delineated in the Operations Manual there are major problems

in completion of forms, and ultimately this has compounded the lack of any data entry of the medical data from the screening process and quality assurance/quality control.

SUGGESTION: It is absolutely essential that a coding manual be developed as soon as possible for all forms that are filled out at any time during the progression of the study. This manual must have in it practical suggestions and examples of how to and how not to fill in data fields as well as explicit codes that can be filled in. Only when this manual has been completed and explained to the various personnel who actually fill in the forms can any attempt be made at quality control and viable data entry. In this regard, two milestones have been suggested for the third quarter: Milestone 7 "Draft Instructions for Filling Out All Study Forms" and Milestone 8 "Draft a Coding Manual for Coding the Study Forms" The compilation of a coding manual for all forms in the study should in fact include instructions for filling out forms.

It was learned at the time of our meetings that the BelAm project is expected to hire Dr. Olga Polyanskay to coordinate quality assurance/quality control as well as updating the Operations Manual. I cannot emphasize too strongly that if she is hired that one of her first tasks should be the compilation of such a manual and the monitoring of form completion/questionnaire administration adhering as strictly as possible to the codes which are pre-assigned on all forms and the instructions as to how forms and questionnaires are completed.

⑤ Equivalence Between Ukraine Thyroid Study and Belarus Thyroid Study: In my first trip report I commented on the need to ensure that the study procedures and data forms in the two studies be as similar as possible so that at the conclusion of fieldwork the two data sets could be combined for data analysis if deemed necessary.

During our meeting, it became evident that there are, in fact, some differences between the two studies. In the Ukraine study, the dosimetry questionnaire is completed by the cohort member at the

time of examination or subsequent to this, by a parent, etc., if the cohort member is of the age that he/she cannot recall events circa April 1986.

In the Belarussian study, it seems two questionnaires, although basically identical, are completed. A self-administered dosimetric questionnaire is sent with the invitation letter to the potential cohort member and he/she then is requested to bring that completed form to the clinic at time of screening. Then the second questionnaire is administered to the cohort member or completed subsequently by the parent and sent back to the clinic. I am somewhat concerned about the equivalence of the dosimetric information between the two studies as it appears that the ascertainment of dosimetric information in Belarus is much more intense than that in Ukraine. In this regard, although the Belarus questionnaire asks the same basic questions as does the Ukraine questionnaire, the former includes many more additional questions.

SUGGESTION: Wherever possible, the questionnaires and the introduction and administration of these questionnaires to cohort members should be identical in both studies.

C. Overall Impressions:

In general I was very encouraged by the work of Dr. Buglova and her group especially with regard to the success they have had in tracing the number of potential cohort members they have and their tenacity in doing so. I was, however, dismayed at the seeming lack of documentation at all phases of the study which would enable the investigators and ourselves to assess accurately progress to date and to evaluate the various mechanisms of cohort identification and recruitment. It is essentially this lack of documentation and monitoring that has compounded the problems associated with data entry and quality assurance/quality controls.